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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/403,539	10/22/1999	NICHOLAS M. DEAN	ISIS-3013	7420

32650 7590 06/03/2003

WOODCOCK WASHBURN LLP
ONE LIBERTY PLACE - 46TH FLOOR
PHILADELPHIA, PA 19103

EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	26

DATE MAILED: 06/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary	Application No. 09/403,539	Applicant(s) Dean et al
	Examiner Jane Zara	Art Unit 1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 21, 2003* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *28, 29, 35, and 36* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *28, 29, 35, and 36* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Office action is in response to the communication filed February 21, 2003, Paper No. 25.

Claims 28, 29, 35 and 36 are pending in the instant application.

Any rejections not repeated in this Office action are hereby withdrawn.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Maintained Rejections

Claims 28, 29, 35 and 36 are rejected under 35 U.S.C. 112, first paragraph, for lacking enablement over the scope claimed for the reasons of record set forth in the Office action mailed October 22, 2002, Paper No. 23.

Applicant's arguments filed February 21, 2003 have been fully considered but they are not persuasive. Applicants argue that adequate disclosure for enabling the claimed invention has been made, which invention comprises the modulation of expression of any target nucleic acid comprising the administration into the alimentary canal (e.g. orally, rectally, endoscopically, sublingually or buccally) of any oligonucleotide which hybidizes to any target nucleic acid, and which oligonucleotide comprises a 2'-O-(2-methoxyethyl) modification, and optionally further comprises a heteroatomic backbone modification, including a methylene(methylimino)

modification. Contrary to Applicants' assertion, the enhanced bioavailability of a 2'-MOE or a 2'-MOE gapped oligonucleotide following alimentary administration is not representative of the ability to modulate the expression of any and/or all target genes comprising administration of such modified oligonucleotides. Applicants assert that the enhanced bioavailability of an oligonucleotide has a greater ability to reach its target site. Contrary to Applicants' assertion, one cannot predict the ability to target and inhibit the expression of a target gene simply because an oligonucleotide has enhanced bioavailability. Enhanced bioavailability indicates that the oligonucleotide has not been degraded, but does not indicate that any and/or all target genes in any and/or all target cells will be successfully reached by the oligonucleotide, whereby target gene expression is modulated. It requires experimentation beyond indication of oligonucleotide bioavailability to determine the efficacy of an antisense oligonucleotide to modulate expression of a target gene. The success of one antisense to modulate its specific target gene via administration by a particular route is not indicative of all antisense to target any and/or all target genes. The incorporation of the claimed modifications do not lessen the unpredictability of achieving efficacy by a particular antisense for a particular target gene.

Applicants argue that the references cited for the unpredictability of antisense have been misinterpreted by the examiner, and that successful clinical trials are an unnecessary burden placed upon Applicants by the PTO. Contrary to Applicants' assertions, no requirement has been made for producing evidence of successful clinical trials in order to enable the scope of the claimed invention. The Pihl-Carey reference has been provided to illustrate that one cannot predict the

success of a particular antisense to reach and inhibit the expression of its intended target gene in vivo without experimentation, nor can one extrapolate the success achieved by an antisense to reach and inhibit its intended target gene to the success of any and/or all antisense to reach their intended target genes in vivo, and the incorporation of a particular modification does not make in vivo success more predictable.

Applicants have provided several references that oligonucleotides in various animal models have been well documented, and that antisense oligonucleotides are shown to unequivocally localize within the cells of various organs, and that, for instance, in 1991 in vivo modulation of N-myc expression using antisense was achieved in mice. The examples and general protocols provided by Applicants do not necessarily predict the efficacy or success of any antisense to appropriately target and inhibit its intended target gene comprising the alimentary administration of 2'-O-(2-methoxyethyl) modified oligonucleotide or optionally further comprising a heteroatomic backbone modification, including a methylene(methylimino) modification. The handful of oligonucleotide antisense molecules that have successfully completed clinical trials provide hope for the efficacy of antisense in providing treatment effects, but undue experimentation is still required for the claimed oligonucleotides of the instant invention.

Applicants additionally argue that the presence of inoperative embodiments within the scope of a claimed invention does not necessarily render the claimed invention nonenabled. The instant invention embodies the ability of any and/or all antisense bearing the modifications claimed

to successfully target and modulate the expression of their intended target gene. The incorporation of modifications does not necessarily enable any and/or all antisense to target and modulate the expression of their intended target genes in vivo. The presence of non-working embodiments is not the question here, rather it is an issue of unpredictability for the broad scope claimed. The example provided and stressed by Applicants, comprising an increase in intestinal absorption of an antisense oligonucleotide that targets human C-raf, is enabling for increasing the intestinal absorption of the modified antisense oligonucleotide in vivo, but is not necessarily enabling for the ability of any antisense oligonucleotide comprising the claimed modifications to successfully target and modulate the expression of its intended target gene in vivo. Enablement of this broad scope requires undue experimentation beyond that existing in the art, and beyond that provided in the instant disclosure. Therefore, the instant invention remains rejected for lacking scope of enablement over the broad scope claimed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ

May 29, 2003

RAM SHUKLA
PRIMARY EXAMINER